Efforts to Control Sexually Transmitted Infections As a Means to Limit HIV Transmission: What Is the Evidence?

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There is overwhelming and compelling evidence that control efforts for sexually transmitted infection (STI) have a major role to play in the prevention of HIV transmission. Community-based randomized controlled trials are set as the highest standard of evidence for showing the efficacy of STI interventions to prevent HIV transmission. The negative results of recent randomized controlled trials have cast doubt on the positive findings of the Mwanza study. Deeper analysis of the result of these trials has improved understanding of the role of STI interventions and augmented the wealth of evidence provided by numerous epidemiologic and biomedical studies. Apart from the biologic impact of effective treatment of curable STIs on HIV transmission, clinical services also support the reduction of HIV risk behaviors. STI interventions should limit the scale of the impending epidemics in Asia and Eastern Europe, depending on the priority that they are given by governments and major donor agencies.

Introduction

Globally, the numbers of HIV infections continues to grow at an estimated 4.8 million new infections per year as of the end of 2003 [1]. Most of these infections are sexually transmitted [1]. Numerous potential cofactors associated with sexual transmission have been identified and include 1) transmission through blood exchange; 2) HIV viral load; 3) nutritional deficiencies; 4) hormonal contraceptives; 5) stage of HIV infection; 6) human leukocyte antigen type; 7) male circumcision status; and 8) sexually transmitted infections (STIs) [2–8]. This review addresses the recent work on STIs and HIV transmission, highlighting advances investigating the epidemiology and biology of HIV transmission, the closer analysis of the conflicting results of the community randomized controlled trials (CRCTs), and the increasing evidence highlighting the role of herpes simplex virus type 2 (HSV-2) in HIV transmission.

There are several reviews that provide excellent overviews on the evidence of the relationship between STI and HIV [9–13]. These reviews cover a large body of cumulative work that overwhelmingly indicate that STIs are important cofactors in HIV transmission. Any meta-analysis of this body of evidence, however, has been hampered by publication bias and wide variation in the design and analysis of individual studies [11]. The biologic evidence supporting the cofactor effect of STIs is focused on the role and mechanisms of STIs increasing infectiousness of and/or susceptibility to HIV infection.

Evidence for Sexually Transmitted Infections Increasing HIV Infectiousness

The role of STIs in increasing the infectiousness of HIV has been inferred from documentation of increased viral secretion or viral replication in the genital tract as a result of local or systemic infection. Numerous studies have documented increased genital shedding with STIs and frequent detection of HIV from STI-related ulcerations [11,13]. More recently data have become available on the effects of HSV-2 infection in women and *Trichomonas vaginalis* infection on increased HIV-1 genital shedding [14–17]. The frequent detection of acute HIV-1 infection in patients presenting for STI care in Malawi suggests that STIs and HIV-1 may often be cotransmitted [18].

In contrast to the many studies documenting increased HIV-1 shedding with STIs, only a handful of studies have been undertaken documenting the impact of STI treatment on HIV shedding [19]. In Malawi and Kenya, HIV-1 RNA concentration in semen and HIV-1 DNA in urethral secretions, respectively, declined in men after treatment [19]. HIV-1 shedding in female sex workers with STIs in Côte d'Ivoire and Kenya were also significantly reduced after treatment [19,20]. In Malawi, the addition of metronidazole to urethritis treatment significantly reduced the excretion of HIV-1 RNA in the semen of men with *T. vaginalis* infection [15].

Reports of changes in plasma HIV-1 viral load as a result of an STI have not been consistent. In Côte d'Ivoire and Kenya, STIs in women were associated with increased HIV-1 blood viral levels that returned to preinfection levels after treatment [21,22]. In Malawi, however, HIV-1 blood viral loads showed no difference before and after treatment of urethritis in men [23]. HSV-2 reactivation, even subclinical disease, and early syphilis markedly influenced HIV-1 plasma viremia that declined after appropriate treatment [24,25]. In addition to potentially increasing the risk of sexual HIV transmission, these increases in viral load associated with acute bacterial STIs and with recurrence of viral infections may also adversely affect HIV disease progression.

Evidence for Sexually Transmitted Infections Increasing Susceptibility

Potentially plausible mechanisms for STIs increasing susceptibility to HIV are outlined below. Through macro- or microulcerations, STIs could disrupt epithelial or mucosal barriers exposing subepithelial lymphocytes and Langerhans cells [26].

Ulcerative and nonulcerative diseases may result in recruitment of HIV target cells into the genital tract or increased expression of HIV coreceptors [27,28•]. STIs might affect local immunity or other local microenvironment changes such as pH, resulting in increased HIV-1 susceptibility [30]. A recent review synthesizes the extensive literature on the complex immunology of the genital tract and HIV-1 [28•].

Ulcerative and nonulcerative STIs have been consistently documented as having strong associations with HIV seropositivity with odds and risk ratios higher for ulcerative STIs [11–13]. Combined-risk estimates for syndromes and for specific STIs on HIV susceptibility have been estimated. The overall effect estimate for nonulcerative disease was 1.7, with gonorrhea, chlamydial infection, trichomoniasis, and bacterial vaginosis estimated at 2.1, 2.2, 1.5, and 1.4, respectively [11]. Similarly, the overall effect estimate for ulcerative disease was 2.7, with chancroid, syphilis, and herpes estimated at 2.1, 2.5, and 2.7, respectively [11].

In addition to the numerous reported studies on bacterial STIs and STI syndromes, there is a growing body of data on the impact of HSV-2 on HIV-1 transmission. A meta-analysis of studies on the effect of HSV-2 infection on HIV-1 acquisition reviewed nine cohort or nested case-control, and 22 case-control or cross-sectional studies [29]. From the cohort studies the risk estimate was 2.1 (95% confidence interval [CI], 1.4–3.2) and was increased in developed and developing countries, for heterosexual men and for men who have sex with men, but not heterosexual women since there was only one reported study in women.

Three recently published studies suggest that the risk of HIV acquisition may be greater with recent HSV-2 infection than with chronic HSV-2 infection. In Tanzania HSV-2 increased the risk of HIV-1 acquisition among persons who seroconverted to HSV-2 in the prior 2 years (adjusted odds ratio [OR], 16.8; 95% CI, 6.1–46.3 for men and adjusted OR, 2.2; 95% CI, 0.8–6.5 for women), which was greater than the corresponding risk associated with chronic HSV-2 infection (adjusted OR, 6.1, 95% CI, 2.5–14.9 for men and adjusted OR, 1.3; 95% CI, 0.6–2.8 for women) [30]. In Pune India, a retrospective cohort study established HSV-2 seroprevalence and seroincidence in 2732 HIV-1 seronegative clients of STIs or gynecology clinics [31•]. Based on a 6-month repeat HSV-2 serologic testing, HSV-2 was categorized as recent incident (in the previous 6 months) or remote incident (more than 6 months) or prevalent. The adjusted hazard ratio of HIV-1 acquisition increased with relative timing of HSV-2 infection from 1.7 (95% CI, 1.2–2.3) among those with prevalent HSV-2 infection to 1.9 (95% CI, 1.2–3.2) among those with remote incident HSV-2 infection to 3.8 (95% CI, 1.8–8.0) among those with recent incident HSV-2 infection. In a nested case-control study of US men who had sex with men, there was a greater trend toward higher risk of HIV acquisition among those with recent HSV-2 infection (adjusted OR, 2.8; 95% CI 0.8–10.1) than those with chronic HSV-2 infection (adjusted OR, 1.8; 95% CI, 1.1–2.9) [32].

These findings are consistent with what is known about HSV-2 infections, notably that the severity of incident HSV-2 infection and the frequency of recurrences are greatest in the first year after acquiring HSV-2. However, the interpretation of these data is confounded by sexual behavior; acquisition of HSV-2 could be a marker for exposure to an HIV-1–infected person who may be shedding HSV-2, more frequently and at higher amounts, than an HIV-1–noninfected person. Currently two clinical trials are under way to test two hypotheses: 1) HSV-2 increases susceptibility to HIV-1 infection, 2) HIV-1 infectiousness is increased by HSV-2. The National Institutes of Health (NIH) are funding one multicenter trial where HSV-2–suppressive therapy will be tested in HSV-2 seropositive persons at risk for acquiring HIV-1 for efficacy in reducing HIV-1 acquisition; HIV Prevention Trial Network Protocol 039 [33]. The Bill and Melinda Gates Foundation is supporting another trial that will test whether HSV-2–suppressive therapy in an individual coinfected with HIV-1 and HSV-2 will reduce HIV-1 transmission [34].

Community-based Randomized Controlled Trials of Sexually Transmitted Infection Treatment to Reduce HIV Transmission

The effectiveness of STI treatment for HIV prevention has been tested in three published CRCTs and one published randomized controlled trial. The underlying hypothesis of these trials was that a reduction in curable STIs, a cofactor in the causal pathway for HIV infection, would reduce HIV transmission. Contrasting results have led to considerable

debate in the literature and a detailed comparative examination of the studies and additional modeling.

Sexually transmitted infection syndromic management in Mwanza, Tanzania

Between 1991 and 1994 in the Mwanza district of Tanzania, a CRCT was conducted to evaluate the impact of improved syndromic-case management of STIs on preventing HIV transmission in the general population [35]. At a 2-year follow-up, a 38% (95% CI, 15–55) reduction in HIV incidence was found. The prevalence of symptomatic urethritis in men was reduced by 50%, and newly acquired syphilis was reduced by approximately 40%, although there was no reduction in gonococcal, chlamydial, or trichomonal prevalence in women [36]. The proportion of new HIV infections attributable to the effects of symptomatic STIs on susceptibility, the population attributable fraction (PAF), was 35.5% for the comparison arm and 4.3% for the intervention arm, strongly supporting the hypothesis that a reduction in symptomatic STIs, a cofactor in the causal pathway, led to a reduction in HIV [37].

Periodic mass treatment in Rakai, Uganda

Between 1994 and 1996, in a 2-year study in the Rakai district of Uganda, a CRCT of periodic, mass STI treatment was given every 10 months and showed no effect on HIV incidence [38]. The investigators documented a significant reduction in *T. vaginalis* in women in the treatment communities but found no significant reduction in the intervention communities compared to the control communities in the prevalence of gonorrhea, chlamydial infection, new syphilis seroreactivity, bacterial vaginosis, or reported interim history of urethral discharge, vaginal discharge, or genital ulceration. The PAF for STI symptoms was 12.4% in the comparison arm and 7.1% in the intervention arm, a nonsignificant difference [39]. A reduction in trichomoniasis was the only cofactor in the causal pathway to be affected.

Sexually transmitted infection syndromic management in Masaka, Uganda

Between 1994 and 2000 in the Masaka district of Uganda, a CRCT with three arms was conducted [40••]. One arm received information, education, and communication (IEC) alone, another arm received IEC and STI syndrome management, and the control arm received community development. HIV-1 incidence did not differ between the groups. The IEC-only arm had a decrease in HSV-2 seroconversion compared to the control arm. The combined IEC plus syndrome management arm had a significant reduction in high-titer incident syphilis and gonorrhea prevalence, and an increase in reported condom use with last casual partner.

Comparison of community-based trials

There has been considerable discussion in the literature on the contrasting results of the Mwanza and Rakai trials. A number of hypotheses have been put forward since the publication of the Rakai trial including study design and population differences [41,42] and the stage of the epidemic. The HIV epidemic in Uganda was more established than in Tanzania, thus influencing both exposure to HIV and distribution of HIV viral load (*ie*, there were more incident HIV infections and more persons with advanced disease in Rakai) [41]. The stage of the epidemic may have also influenced the relative prevalence of incurable STI syndromes such has HSV-2 genital ulceration [41]. Symptomatic STIs may exert a stronger cofactor effect than asymptomatic STIs; therefore, the continuous availability of syndrome treatment resulted in higher coverage of symptomatic STIs than did mass treatment [41]. Household-based mass therapy may have resulted in lower coverage of higher–risk individuals in the communities [42]. Prevalence rates of STIs in Rakai were not significantly reduced for most infections, suggesting reinfection between rounds of mass treatment. This may also be an indication of the mobility of high-risk subpopulations, individuals from which may have been present at one round of follow-up and not the other, and who may have had regular sexual partners outside of the intervention areas.

With the publication of the Masaka trial in which syndrome management had no impact on HIV incidence, the underlying differences in the populations were thought to play significant roles in the trial's outcomes. A reanalysis of baseline data from the three trials was undertaken comparing demographics, sexual risk behavior, and HIV/STI epidemiology with reported STI prevalence data adjusted for the performance characteristics of the diagnostic techniques used [43,44•]. This analysis found similar demographics but higher sexual risk behavior in Mwanza compared to the Uganda sites with younger age of male sexual debut, more sexual partners reported in the last year, and much lower condom use in casual partnerships. The stages of the HIV epidemics were vastly different in each of the sites as documented by HIV prevalence (Rakai 16.5%, Masaka 12.1%, and Mwanza 3.8%) and incidence (Rakai 1.5/100 person-years, Masaka 1.1/100 person-years, and Mwanza 1.0/100 person-years). Because of migration issues, HIV prevalence and incidence were most likely underestimated in all three trials. Prevalence of sexually transmitted infection was underestimated in all three trials but especially in the Mwanza trial because of diagnostic errors and selection bias. After adjustment, the prevalence of gonorrhea, trichomoniasis in females, chlamydial infection in females, and high titer syphilis (>1:8) was higher in Mwanza than the Ugandan sites. HSV-2 and syphilis seroprevalence and chlamydial prevalence in men were similar across all sites. The higher prevalence of risk behaviors and curable STIs in Mwanza may help explain the contrasting results of these trials. Results of a simulation of Mwanza and Rakai showed that the highest PAF in Mwanza was from chancroid (43%) alone, which was higher than the total PAF for all STIs including HSV-2 (38%) in Rakai [45].

Modeling of the Rakai data has concluded that the impact of STI treatment interventions on HIV transmission may depend more on behavior-risk modification and reduction of the population than on the stage of the epidemic and that, even in advanced epidemics where there is little behavior change, STI treatment may still be an important intervention [46].

Randomized Controlled Trial Presumptive Treatment in Kenya

In Nairobi between 1998 and 2002, HIV-negative female sex workers (FSWs) were treated monthly with 1 gram of azithromycin or placebo; all were provided counseling, free condoms, STI case management, and full STI screening and treatment every 6 months [47••]. At the end of the study period with 2 or more years of follow-up, there was no difference in HIV incidence between the treatment and placebo groups (4% vs 3.2%, respectively). There was a significant decrease in the incidence of gonococcal and chlamydial infection and trichomoniasis in the treatment group compared to the placebo group, but no difference in bacterial vaginosis, syphilis, or genital ulcer disease incidence. Incident HIV infection was associated with preceding *N. gonorrhoeae* infection (rate ratio, 4.9; 95% CI 1.7–14.3). The study also documented a highly significant reduction in HIV risk behavior (increased condom use and decreased client numbers) in all study subjects regardless of study arm [48]. Possible reasons postulated by the authors for the inconsistent results within the trial include the high level of care afforded to all participants that may have reduced the HIV seroconversions attributed to STIs and the high level of risk reduction exhibited by the participants. In fact, the observed HIV seroconversion rate of approximately 4% in this population was much less than the expected 15% per year used in the sample size calculations. The authors also point out other causal pathways that may account for the observed association between STIs and HIV-1 seroconversion including increased viral shedding in male clients coinfected with HIV-1 and STIs, a disproportionately high prevalence of STIs in HIV-1–infected men, and enhanced susceptibility to STIs in HIV-1–infected FSWs.

Conclusions

Evidence including biologic data, observational studies, controlled trials, and modeling from the past several years adds much to existing knowledge of the association between STIs and HIV transmission. The synergistic, biologic relationship between HIV and STIs is little disputed with the vast body of evidence indicating that STIs that cause ulcerations or mucosal inflammation contribute to the spread of HIV by increasing susceptibility, infectiousness, or both. However, the programmatic implications of STI control as an intervention to reduce HIV transmission have been difficult to prove experimentally. Three of the four trials done to examine this question have shown no impact of STI treatment on HIV transmission (*eg*, HIV infectiousness or susceptibility to HIV in the community-based trials or susceptibility to HIV in the Kenyan FSW trial). However the complexity of these studies requires a careful interpretation of the evidence as discussed earlier. Of the four trials, only one was conducted under conditions of relatively high STI prevalence. The other three took place where behavior change and/or STI interventions had already reduced the prevalence of curable STIs and had less impact on STI rates and no impact on HIV. The Kenya site, for example, had had a longstanding, effective HIV/STI intervention, which had already had a marked impact; HIV prevalence was in decline and the rates of curable STIs, especially ulcerative STIs, had fallen to low levels compared to FSW populations in other developing countries [49]. The untested role of HSV-2 in all of these trials is a constant subtheme in the discussion of these trials.

The vast majority of the world's population lives in countries experiencing rapid increases in STIs and HIV (*ie*, India, China, Indonesia, Southeast Asia, Eastern Europe, and Russia), have high STI prevalence in high-risk subgroups, and have poor to nonexistent STI services [1]. Even with the limited clinical trial data to date, it appears that STI treatment services reduce HIV incidence (susceptibility and infectiousness) in environments where HIV prevalence is growing, where STI treatment services are poor, and where STIs are prevalent. A focus on STIs as a component of HIV comprehensive prevention efforts in these rapidly emerging epidemics is important. Quality STI prevention and care programs also support the reduction of HIV risk behaviors: condom use with last casual partners increased in Masaka and participants in the Kenya trial showed marked reduction in risk behaviors. Comprehensive STI care includes treatment and prevention components of partner reduction, partner treatment, and condoms. Surveillance data show parallel declines in curable STIs and HIV after implementation of comprehensive STI interventions (both curative and prevention services) in Thailand, Cambodia, and Nairobi, Kenya [50,51]. While further research must define the most effective STI intervention strategy and the critical STIs for intervention, moving forward with current knowledge is essential.

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